Remarks

Applicants thank the Examiner for withdrawing the rejections of claims 22, 45, 48, 1-21, 23-44, 46-47, 49-63, 68, and 80 due to the abandonment of 10/687,374. The Examiner is also thanked for withdrawing the rejections of claims 1-44, 46, 49-52, 54-55, 63, and 80 due to the amendment of the application. Applicants also appreciate the allowance of Claim 53 in the instant application.

The Claims currently pending in this application are 1-55, 58, 63-70, and 80-89. Claim 53 has been allowed. Claims 64-70, and 81-89 have been withdrawn from consideration. Claims 1-52, 54, 55, 58, 63 and 80 have been rejected by the Examiner in the Office Action of July 21, 2006. Responses to the Examiner's rejections are contained herein. In addition, the Applicants amend the Specification and the Claims as described herein.

Amendments to the Specification

Applicants currently amend the Specification with matter contained at least in Claim 49 of the originally filed application. This amendment was suggested by the Examiner in the Office Action of July 21, 2006 to provide a definition for "P" in the Specification. Applicants maintain that no new matter is being added to the application by this amendment.

Amendments to the Claims

Claim 21 is amended by the addition of a period at the end of the Claim. Claim 24 is amended by the correction of a typographical error. Applicants maintain that no new matter has been added by either of these amendments.

Applicants present new Claims 90-97 that are supported in the application as described herein.

Claim 90 is supported by the original Specification, page 3, lines 22-29 through page 4 lines 1-29, that was subsequently amended in the Response of August 2, 2005 but with the exclusion of

the term "prodrug" in the current amendment. Examples of non-prodrugs reading on this claim in the original application are, at least, Examples 2, 9, 11, 15, 17, 18, 19, 21, 22, 24, 25, 48, 51, 52, 53, 58, 60, 62, 64, 66, 68, 70, 76, 79, 145, 147, 204, 206, 230, 232, 234, 236, 238, 240, 276, 280, 284, 285, 287, 289, 290, 296, 298, 300, 306, 308, 310, 313, 317, 318, 319, 320, 321, 322, 155, 165, 292, and 314. Applicants maintain that Claim 90 is adequately supported by these Examples.

Claim 91 depends from Claim 90 and further narrows the definition of A^1 as supported by the definitions for the alternatives for A^1 in Claim 90. Further support for Claim 91 is found in the Examples cited as supporting Claim 90 above. These Examples include, at least, 48, 51, 52, 53, 79, 230, 232, 234, 236, 238, 240, 276, 280, 284, 285, 287, 289, 290, 306, 308, 313, 317, 318, 319, 320, 321, 322, 292, 314 and 206. Applicants maintain Claim 91 is adequately supported by Claim 90 and the Examples cited.

Claim 92 depends from Claim 90 and further narrows the definition for X in Formula I. One of the definitions for X in Claim 90 is O. Formula I is supported in the original Specification at page 28, line 6. Further support for Claim 92 is found in all of the Examples cited as supporting Claim 90. Applicants maintain that Claim 92 is adequately supported by Claim 90, the Specification, and the Examples cited.

Claim 93 depends from Claim 92 and further narrows the definitions of L and Ar. The narrowed definitions for L and Ar are found among the alternatives for these variables in Claim 90. Further support for Claim 93 is found in all of the Examples cited as supporting Claim 90 with the exception of Examples 310 and 313. Applicants maintain that Claim 93 is adequately supported by Claims 90 and 92 and the Examples cited.

Claim 94 depends from Claim 92 and further narrows the definitions of A^1, R^2, R^3, and R^4. The narrowed definitions for A^1, R^2, R^3, and R^4 are found among the alternatives for these variables in Claim 90. Further support for Claim 94 is found in all of the Examples cited as supporting Claim 91 with the exception of Example 206. Applicants maintain that Claim 94 is adequately supported by Claims 90 and 92 and the Examples cited.

Claim 95 depends from Claim 90 and further narrows the definition of X in the Formula. One of the definitions for X in Claim 90 is O. The Formula is supported in the original Specification at page 30, line 3. Further support for Claim 95 is found in all of the Examples cited as supporting Claim 91 with the exception of Example 206. Applicants maintain that Claim 95 is adequately supported by Claim 90, the Specification and the Examples cited.

Claim 96 depends from Claim 95 and further narrows the definitions of L and Ar. The narrowed definitions for L and Ar are found among the alternatives for these variables in Claim 90. Further support for Claim 95 is found in all of the Examples cited as supporting Claim 91 with the exception of Example 206. Applicants maintain that Claim 96 is adequately supported by Claims 90 and 95 and the Examples cited.

Claim 97 depends from Claim 96 and further narrows the definition of R^2, R^3 and R^4. The narrowed definition for R^2, R^3 and R^4 (H) is among the alternatives specified for these variables in Claim 90. Further support for Claim 95 is found in all of the Examples cited as supporting Claim 91 with the exception of Example 206. Applicants maintain the Claim 97 is adequately supported by Claims 90, 95, and 96 and the Examples cited.

Applicants submit that no new matter is being introduced by these amendments. More specifically, the subject matter of the new Claims are limited to the non-prodrugs of the original Claims that covered both prodrugs and non-prodrugs. New Claim 90 could have been written in dependent form from Claim 1 and Claims 91-97 depend from Claim 90. Therefore, Applicants believe that the entry of these amendments would not burden the Examiner with additional searching. Applicants herein respectfully request the entry of these amendments in the instant application.

Rejection of Claim 49 under 35 U.S.C. 112, first paragraph

The Examiner has rejected Claim 49 under 35 U.S.C., first paragraph, for alleged lack of written description in the Specification on the basis of a lack of written definition for the term "P" in this Specification. As suggested by the Examiner, Applicants have amended the Specification by copying the language of original Claim 49 to page 17 before line 6. Original Claim 49 contains a definition for "P" as a protecting group selected from benzyhydryl ($CHPh_2$), trialkylsilyl (R_3Si), 2-trimethylsiloxyethyl, alkoxymethyl (CH_2OR), and ester (C(=O)R). No new matter was added by this amendment.

Because the Specification as amended now contains a definition of "P", Applicants respectfully request that the rejection of Claim 49 based on 35 U.S.C. 112, first paragraph, be withdrawn.

Rejection of Claims 1-44, 46, 50-52, 54-55, 58, 63, and 80 under 35 U.S.C. 35 112, first paragraph

Claims 1-44, 46, 50-52, 54-55, 58, 63, and 80 were rejected by the Examiner under 35 U.S.C. 112, first paragraph, because of an alleged lack of enablement for making prodrugs of the claimed invention. Further, the Examiner alleged that the claims contain subject matter which is not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. Applicants respectfully traverse this rejection.

The Examiner has characterized "person skilled in the art to which it pertains" in the language of the first paragraph of 35 U.S.C. 112 as being one skilled in the art of medicinal chemistry. As the Examiner has cited Wolff's characterization of artisans involved in making prodrugs as being a collaborative team of synthetic pharmaceutical chemists and metabolism experts, Applicants believe the Examiner intended to include such artisans in the characterization of "one skilled in the art of medicinal chemistry" and further maintain that this would include those skilled in pharmcokinetics and others skilled in the art of pharmaceutical development.

The Examiner has cited the factors in determining enablement from *In re Rainer,* 146 USPQ 218 (1965), *In re Colianni,* 195 USPQ 150, and *Ex parte Formal,* 230 USPQ 546 that include (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working examples, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in that art, (g) the predictability or unpredictability of the art, (h) and the breadth of the claims. Further, the Examiner's views on how the instant application does or does not meet those factors were then described. Applicants herein address each of these factors in traversing this rejection.

(a) Quantity of experimentation:

The Examiner alleges that undue experimentation would be required to obtain the prodrugs of the instant invention. Applicants respectfully disagree. As described in MPEP 2164.06 and supported by *in re Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977), an extended period of experimentation is not undue if the skilled artisan is given sufficient direction or guidance. Further, *in re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988), asserts that a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed.

Applicants respectfully assert that the Specification is enabling for the skilled artisan to practice the instant invention. Undue experimentation would not be required to practice the invention. Direction and guidance can be found in the Specification for the preparation of the prodrugs of Applicant's invention. For example, preparations of working examples of ester prodrugs 3, 23, 72, and 74 are found at pages 156, 168, 195, and 196, respectively. Preparation of a working example of an ether prodrug 8 is found at page 159. Preparations of a working examples of phosphate ester prodrugs 26, 148, 151, 157, 158, 160, 169, 170, 184, and 189 are found at pages 169, 240, 241, 244, 245, 246, 251, 252, 259 and 262, respectively. Preparation of at least one example of a phosphonate amide prodrug 177 is found at page 255. Preparations of sulfamate prodrugs 55, 125, and 128 are found at pages 285, 227, and 228, respectively. Preparations of sulfonate prodrugs 263, 265 and 274 are found at pages 308, 309, and 314, respectively. The

numerous prodrug examples would enable one skilled in the art to prepare the range of prodrugs comprising this instant invention.

Descriptions of assays and methods of determining the chemical, enzymatic and biological stabilities of prodrugs in human and animal tissues are known in the art. For instance, Oliyai, et al, *Pharmaceutical Res.* (1999) 16:1687-1693 at page 35, line 15 of the Specification; Krise, J. and Stella, V., *Adv. Drug Del. Reviews* (1996) 19:287-310 at page 35, line 16 of the Specification; Bischofberger et al., U.S. Patent no. 5,798,340 at page 35 line 17 of the Specification; Oliyai, et al., *Intl. Jour. Pharmaceutics* (1999) 179:257-265 at page 36, line 2 of the Specification; Yuan, et al., *Pharmaceutical Res.* (2000) 17:1098-1103 at page 36, line 3 of the Specification; Darby, G., *Antiviral Chem. & Chemotherapy* (1995) Supp. 1, 6:54-63 at page 36, line 15 of the Specification; and Beauchamp, et al., *Antiviral Chem. Chemotherapy* (1992) 3:157-164 at page 37, line 9, would all adequately instruct the pharmaceutical chemist, metabolic chemist, pharmacokineticist, clinical chemist, and others skilled in the art of pharmaceutical development how to practice the prodrug aspects of the instant invention. Copies of these articles are included in this response as a courtesy to the Examiner with the exception of U.S. Patent no. 5,798,340 that is of record.

The Examiner is respectfully referred to MPEP 2164.05(b) and cases cited therein, wherein it is indicated that when an invention involves distinct arts, the specification is enabling if it enables those skilled in each art to carry out the aspect proper to their speciality. As indicated above with references and working examples, the medicinal chemist, pharmaceutical chemist, metabolic chemist, pharmacokineticist, clinical chemists, and others skilled in the art of pharmaceutical development are all adequately instructed by the Specification in how to practice the prodrug aspects of the instant invention in their specialities. Because the instructions in the Specification are enabling to the range of those skilled in the art, undue experimentation would not be required to practice the prodrugs aspects of this invention even if substantial experimentation is required.

(b) Direction concerning prodrugs:

The Examiner points out directions concerning prodrugs are found in the Specification on pages 7-8. The Examiners attention is respectfully drawn to additional disclosures concerning prodrugs in the Specification at pages 35-38 and the references cited therein. This would include assays and methods for determining the chemical, enzymatic and biological stabilities of prodrugs in human and animal tissues. Further direction is provided by the general methods for synthesizing prodrugs of this invention on pages 60-148 of the Specification. In addition, more direction is provided by the working examples of the syntheses of prodrugs by, at least, Examples 3, 8, 23, 72, 74, 26, 148, 151, 157, 158, 160, 169, 170, 184, 189, 177, 55, 125, 128, 263, 265, and 274 in the Specification. This disclosure provides sufficient direction to the skilled artisan and adequately addresses all aspects of prodrug development including assays and methods used by those skilled in the art for selecting and developing a prodrug.

(c) Working examples

The Examiner asserts that there are no working examples of prodrugs in the Specification. The Examiner's attention is respectfully drawn to, at least, examples 3, 8, 23, 72, 74, 26, 148, 151, 157, 158, 160, 169, 170, 184, 189, 177, 55, 125, 128, 263, 265, and 274 in the Specification. Each of these is an example of a prodrug of this invention as defined in the Specification in pages 7-8, and 35-38.

(d) Nature of the invention:

The Examiner asserts that the nature of the invention is the clinical use of compounds and the pharmacokinetic behavior of substances in the human body. Applicants respectfully disagree and assert that the Claims define the invention. All Claims currently being examined are directed to compounds, compositions, or processes for the preparation of compounds. All methods of use Claims have been withdrawn by the Examiner. The Examiner has not rejected the Claims for compounds, compositions, and processes for the preparation of compounds that

are useful for treating HCV infection in the application. The Claims at issue are only those directed to the prodrugs of these compounds, compositions, and processes that are a part of this invention.

(e) State of the prior art:

The Examiner recites the summary of the state of the prodrug art as described by Wolff, Manfred E. in "Burger's Medicinal Chemistry, 5ed, Part 1", John Wiley & Sons, 1995. The Examiner maintains that the reference indicates that there is a low expectation of success in prodrug development, animal models are inadequate for extrapolating data between species, and that the lack of any standard pharmacokinetic protocol is an issue in prodrug development. Applicants respectfully disagree. Applicants assert that the skills and assays described by Wolff for prodrug development differ little from classical drug development, there is a reasonable expectation for success in the development of the prodrugs of the Applicant's invention, and that artisans skilled in prodrug development would possess the general knowledge required for determining which compositions in Applicant's application were appropriate for prodrug development.

Those skilled in the art of prodrug development at the time of Applicant's invention would have had a reasonable expectation for success in developing Applicant's claimed prodrugs. The skilled artisan possessed knowledge of the steps required in prodrug development and had access to tests and assays that would have enabled him to develop the claimed prodrugs with only routine experimentation. The Examiner's attention is directed to a more recent edition of "Burger's Medicinal Chemistry, 6th ed.", John Wiley & Sons, 2003 that characterizes the prodrug art just prior to the filing of Applicant's instant application. In Chapter 14, Volume 2, pages 499-532, Balant, describes a large number of successful prodrugs, including different types of prodrugs, and the pharmacokinetic and biopharmaceutical aspects of prodrug development. The Examiners's attention is also directed to a review by Testa, Bernard, et al., *J. Med. Chem.* **2004**, *47*, 2393-2404 that relies on references published before the filing of Applicant's application. Testa's review also describes many successful prodrugs. The number of prodrugs described and the percentage of drugs characterized as prodrugs in these two publications indicates that there was a reasonable expectation for the successful development of Applicant's claimed prodrugs

contemporaneous with the filing of Applicant's application. Copies of the articles cited are included in this response as a courtesy to the Examiner.

Determination of drug concentrations and metabolism is a factor in drug and prodrug development. The processes in prodrug development compare to normal drug development. The Examiner's attention is again directed to "Burger's Medicinal Chemistry, 6th ed.", John Wiley & Sons, 2003. Chapter 13, pages 431-498, describes the Principles of Drug Metabolism. Chapter 13 is directed to drugs in general, not just prodrugs. The chapter describes the many ways in which drugs can be metabolized, references articles with assays for determining metabolites, describes in vitro methods used to predict in vivo metabolism, and addresses the issue of extrapolating among species when predicting metabolism in man. A comparison of the assays and issues in Chapter 13 with those described by Balant in Chapter 14 would detect only minor differences. Copies of the chapters cited are included in this response as a courtesy to the Examiner.

The many references to the development of prodrugs in both Balant's and Testa's articles also provide many examples of assays used to develop prodrugs, including assays that would be used in pharmacokinetic studies. In addition, Applicant's application also contains references to such assays as described in (a) "Quantity of experimentation" above. Taken together, these references show that one skilled in the art of prodrug development possessed the knowledge required for developing the prodrugs of the Applicant's invention without undue experimentation.

(f) Relative skill of those in the prodrug development art:

The Examiner cites Wolff's characterization of those artisans making prodrugs. Applicants concur with Wolff's description of the skill levels for those skilled in prodrug development but these skill levels are not appreciably different from those skilled in the art of standard drug development as supported in the references in (e). As described in (a), (b), (c), and (e) above, the skilled prodrug artisan is enabled by Applicant's Specification and the general level of knowledge in the art to synthesize, detect and develop the prodrug compositions that are one of the subjects of the instant application without undue experimentation.

(g) Predictability of the art:

The Examiner implies that the scope of the enablement in Applicant's application is not adequate because of the unpredictability of the prodrug development art. The Applicants respectfully disagree. As developed in (e) above, the predictability of the prodrug art varies little from that of standard drugs. As also developed in (a), (b), (c), (e) and (f) above, the general knowledge of the artisan in prodrug development and the direction afforded by the Applicant's Specification would enable one skilled in the art to make, detect, and develop the prodrugs that are one of the aspects of the instant application without undue experimentation.

(h) Breadth of claims:

The Examiner implies that the Specification does not sufficiently enable the breadth of the prodrugs Claims in the application. The Applicants respectfully disagree. Many instances of the syntheses of prodrugs are found in the Specification. For example, the preparations of working examples of ester prodrugs 3, 23, 72, and 74 are found at pages 156, 168, 195, and 196, respectively. Preparation of an ether prodrug 8 is found at page 159. Preparations of phosphate ester prodrugs 26, 148, 151, 157, 158, 160, 169, 170, 184, and 189 are found at pages 169, 240, 241, 244, 245, 246, 251, 252, 259 and 262, respectively. Preparation of phosphonate amide prodrug 177 is found at page 255. Preparations of sulfamate prodrugs 55, 125, and 128 are found at pages 285, 227, and 228. Preparations of sulfonate prodrugs 263, 265 and 274 are found at pages 308, 309, and 314. In addition, general direction to the syntheses of prodrugs of this invention are found on pages 60-148 of the Specification This disclosure would enable a medicinal chemist skilled in the art to prepare the range of prodrugs comprising this instant invention.

As directed in MPEP 2164.01 (a) and as supported *in re* Wands, 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407, it is improper to base a finding of lack of enablement on less than all of the factors discussed above. The above arguments and references demonstrate that one skilled in the prodrug art is given sufficient direction and guidance in Applicant's Specification for the

syntheses, detection, evaluation, and development of the prodrug compositions of Applicant's invention in Claims 1-44, 50-52, 54-55, 58, 63, and 80. In combination with the general skill of the prodrug artisan, such an artisan would be fully capable of practicing the instant invention without undue experimentation. Based on the points directed to the Examiner's attention herein, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-44, 46, 50-52, 54-55, 58, 63, and 80 based on 35 U.S.C. 112, first paragraph.

Rejection of Claims 1-44 based on second paragraph of 35 U.S.C. 112:

The Examiner has rejected Claims 1-44 based on 35 U.S.C. 112, second paragraph as being indefinite due to a lack of a definition for "protecting group". The Specification has been amended in this response to define "P" as a protecting group selected from benzyhydryl ($CHPh_2$), trialkylsilyl (R_3Si), 2-trimethylsiloxyethyl, alkoxymethyl (CH_2OR), and ester ($C(=O)R$). Applicants maintain that the Specification, as amended, contains an adequate definition of a protecting group. Applicants respectfully request that the Examiner's rejection of Claims 1-44 based on 35 U.S.C. 112, second paragraph be withdrawn.

Provisional rejection of Claims 1-49, 54-55, 58 and 80 due to obviousness-type double patenting:

The Examiner has provisionally rejected Claims 1-49, 54-55, 58 and 80 due to an alleged obviousness-type double patenting over claim 24 of US 2006/0116356. Applicants acknowledge the Examiners provisional rejection. Applicants request that the Examiner use the procedure described in MPEP 822.01 wherein the instant application is issued as a patent upon determination of allowable subject matter.

New Claims 90-97:

Claims 1-44, 46, 50-52, 54-55, 58, 63, and 80 have been rejected by the Examiner based on their claims to prodrugs. New Claims 90-97 are directed to the subject matter of Claim 1 but exclude claims to prodrugs. The new Claims are well supported in the Specification as discussed above

and should require no additional searching by the Examiner. Applicants maintain that the current Amendment in the Specification has obviated all rejections in the application that could be applied to Claims 90-97. Therefore, Applicants submit that Claims 90-97 are in condition for allowance, which action they respectfully solicit.

Conclusion

Applicants have amended the Specification, amended the Claims, and responded to each and every point of rejection issued by the Examiner as described above. New Claims 90-97 have been presented and their entry in the instant application respectfully requested. On the basis of the amended Specification, amended Claims, references and arguments presented herein, Applicants now believe that the application is in condition for allowance, which action they respectfully solicit. As all composition claims are now in condition for allowance, rejoinder of the combination and methods Claims 64-70 and 81-89 are respectfully requested.

Applicants authorize charges to deposit account 07-1250 for a two month extension in the instant response and any additional charges occasioned by this response.

Respectively yours,

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